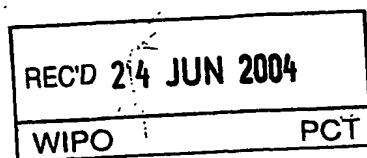


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ELSŐBBSÉGI TANÚSÍTVÁNY

Ügyszám: P0301154

A Magyar Szabadalmi Hivatal tanúsítja, hogy

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Magyarországon

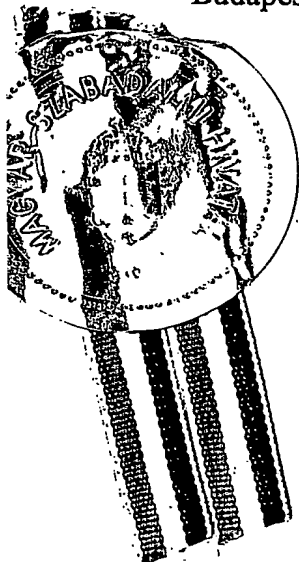
2003. 04. 28. napján 16193/03 iktatószám alatt,

Gyógyszerkészítmény

című találmányt jelentett be szabadalmazásra.

Az idefűzött másolat a bejelentéssel egyidejűleg benyújtott melléklettel mindenben megegyezik.

Budapest, 2004. év 06. hó 04. napján



A kiadmány hitelül: Szabó Emilné osztályvezető-helyettes

The Hungarian Patent Office certifies in this priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application.

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2003-04-28

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New Pharmaceuticals.

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NEW PHARMACEUTICALS.

The invention relates to new biologically active chemical compounds, methods for their preparation, pharmaceutical compositions containing the same and methods for their use. More particularly the objects of the invention are 2-

sterically hindered alicyclic-amine-substituted-4-carboxamido-benzimidazoles, their salts, their synthesis, their use as new PARP-inhibitors and antioxidants, as well as compositions comprising the new compounds for direct medical use and the use of the new compounds as intermediates for further useful chemicals. The new compounds comprise two different bioactive functions - a sterically hindered pyrroli(di)ne or piperidine and a 4-substituted-benzimidazole ring; as a consequence they show both PARP-inhibiting and antioxidant activities.

Abbreviations used in this specification:

PARP = poly(ADP-ribose)polymerase = poly-adenyl-ribosylase

NAD = nicotinamide adenine nucleotide

TBAR = thiobarbituric acid reacting substances

ROS = Reactive Oxidative Species

RNS = Reactive Nitrogen Species

PARP-inhibitors = compounds inhibiting PARP

The first objects of the present invention are compounds of the general formula (I) - where in the formula

R¹ represents hydrogen, an alkyl or alkoxy group

R² represents hydrogen, an alkyl, carboxyl, alkoxy carbonyl, carboxamido or aryl group or a hetero-aryl group

R³ represents hydrogen, alkyl, aryl-methylene, or aryl group

Y is a valency bond, a straight or branched alkene group, carbonylaminoalkene group, containing 1 to 4 carbon atoms, spaced or not spaced by an arylene group

5 n is zero or 1

 Q represents hydrogen, a hydroxyl group or oxygen
 radical (O[·])

 Z represents a single or double bond.

10 In this specification the meaning of the above substi-
 tuents is always the same and they are therefore not repeated
 herein.

15 The new compounds of the invention can be used per se as
 the basis for pharmaceutical media especially as protective
 agents against several forms of diseases caused by Reactive
 Oxidative Species (ROS) and Reactive Nitrogen Species (RNS) or
 diseases which are based on PARP activation or both. They can
 also be used as intermediates in the chemical production of
 medically effective materials in the same field.

20 It is known that the final cause of cell damage in the
 case of vascular diseases is the oxidative stress of the endo-
 thelial cells and of the blood cells (thrombocytes and red
 blood cells). Oxidative stress causes lipid peroxidation, and
 this destroys the structure of the lipid bilayer of plasma
 membrane, which damages ion transport proteins. In ischemic
25 neurodegenerative damages Ca²⁺ overload, ROS and RNS are the
 main contributors. The ROS, e.g. H₂O₂ induces both sodium and
 calcium influx into the cells. In the presence of iron, the
 oxidizing agent hydrogen peroxide produces lipid peroxidation
 and at the same time increases the intracellular calcium con-
30 centration. Thus, in the presence of hydrogen peroxide, paral-
 lel measurements of lipid peroxidation and concentration of
 intracellular free calcium ion are appropriate methods for the
 determination of oxidative cell destruction. [Detection of
 lipid peroxidation is possible by way of methods using thio-
35 barbituric acid reacting substances (TBAR). Intracellular free
 calcium ion can be determined by using a fluorescent intracel-
 lular calcium indicator.]

5 It is also known that PARP is a nuclear protein that is a critical component of the cellular response to DNA damage. There is considerable evidence suggesting that PARP inhibitors can play an important role in repair of DNA damage. Several PARP inhibitors were therefore synthesized and have shown ef-
 10 ficacies in several animal disease models of cancer, ischemia and inflammation. Various 2-substituted-4-carboxamido-benzimidazoles, mono- and bicyclic carboxamides, bi-, tri- and tetracyclic lactams and some other heterocyclic molecules were proposed as PARP-inhibitors (J.Med.Chem. 2003.46.210-213; Re-
 15 view: Idrugs 2001.4(7):804-812). However, none of them contain alicyclic stable nitroxide or its amine precursor functions.

We experienced earlier that certain sterically hindered amines e.g. 2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid [3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-
 20 amide with antiarrhythmic activity metabolized to the corresponding non-toxic nitroxide: 1-hydroxy-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid [3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-amide (J. Med. Chem., 1986, 29, 1138-1152., Free Rad. Biol. & Med., 1997, 22, 909-916). Both
 25 compounds exhibit reduction of the oxidative damages caused by reactive oxidative intermediates formed during reperfusion.

It was also demonstrated before that when certain other antiarrhythmic drugs, e.g. mexiletine, tocainide were modified with a sterically hindered alicyclic nitroxide or its precursor amine the molecules not just preserved or even enhanced
 30 their antiarrhythmic activity but gained a strong antioxidant effect by which they turned capable of an *in situ* scavenging *in statu nascendi* of those highly reactive ROS and RNS which are responsible for oxidative damages (J. Pharmacol. Exp.
 35 Ther. 2000, 292, 838-845 ; J. Pharmacol. Exp. Ther. 2000, 295, 563-571). It is also known that a great variety of sterically hindered 5- and 6-membered nitroxides and their amine precursor

5 sors protect against damages caused by H_2O_2 and radiation (*J. Med. Chem.* 1998, 41, 3477-3492).

The basis of the present invention was the recognition that properly designed sterically hindered amines and their oxidized derivatives are capable to fulfill similar antioxi-
10 dant function as e.g. do sterically hindered phenols, indoles, sulfides and disulfides. This is shown by the reaction scheme A (Figure 3).

The sterically hindered amines and non-toxic radicals may offer the exceptional advantage that they can fulfill the
15 function of multi-step protectors in an antioxidant cascade system. The sterically hindered pyrroli(di)ne or piperidine-*N*-oxyl derivatives comprised in the compounds of general formula (I) and their amine precursors of general formula (Ia) according to the present invention exhibit a protective effect
20 against damages caused by H_2O_2 and other reactive oxygen species; they also exhibit a cardioprotective effect. In addition the presence of a 4-carboxamido-benzimidazole-group in the same molecule makes these compounds capable to inhibit the damages of DNA via inhibition of the PARP activity.

25 Thus it is another basis of the present invention that the new molecules containing both of these functions exhibit both a high PARP-inhibiting activity and a capability for scavenging damages caused by toxic ROS and RNS events.

The new compounds of the general formula (I) according to
30 the invention are capable to exist in two forms namely the form of general formula (Ia) and the form of the general formula (Ib) (see Figure 2).

The sterically hindered amines of general formula (Ia) according to the invention metabolize in the organism to the
35 corresponding nitroxides of general formula (Ib) which equilibrate to diamagnetic *N*-hydroxyl compounds of general formula (Ic) or can be oxidized further up to oxoimmonium compounds of

5 general formula (Id). The N-hydroxyl is able to be oxidized back to nitroxide.

All forms of the compounds of the general formula (I) namely amines of the general formula (Ia), nitroxides of the general formula (Ib), N-hydroxyl compounds of the general formula (Ic) and the oxoimmonium compounds of the general formula (Id) and salts of these compounds are subject of the present invention.

Both the amines and the N-hydroxyl compounds are water-soluble in their salt form, formed with pharmaceutically acceptable mineral acids or organic acids. Such salts are the hydrochlorides, hydrobromides, sulphates, phosphates, phosphites, borates, lactates, ascorbates, acetates, fumarates, formiates, oxalates, tosylates, tartarates, maleates, citrates, gluconates, besylates etc. The salts represent subjects of the present invention. However in addition to the above salts other salts with mineral or organic acids may be of technological use on the course of preparation of the products. Such salts include e.g. the oxalates. Also the technologically useful salts are subjects of the present invention.

25 The combination of two different types of biologically active molecules according to the invention results in a scavenger-type drug with functions of antioxidants in cascade of defence combined with PARP inhibiting effects. This is verified in the biological examples presented concerning compounds of the general formula (I) according to the invention.

30 Thus first objects of the present invention are new compounds of the general formula (I) and their pharmaceutically acceptable salts.

Compounds according to the invention contain along with 35 the substituted benzimidazole a piperidine, pyrrole or a pyrrolidine ring as the heterocyclic ring. These are tetramethyl-substituted, and may contain further substituents such as trifluoro-methyl-phenyl-, hydroxy-, acetyl-, alkoxy-groups. The

5 compounds contain benzimidazole-carboxamide groups which can be primary acid amides or secondary acid-(alkylated) amides.

Preferred compounds are those where the substituents contain C₁₋₄ alkyl as alkyl, C₁₋₄ alkoxy as alkoxy, C₁₋₄ alkoxy-carbonyl as alkoxycarbonyl, 6 or 12 membered aryl as aryl,
 10 piperidine, pyrrole or pyrrolidine groups as heteroaryl groups, a C₁₋₄ alkene as alkene, 6 or 12 membered arylene as arylene groups in any of the substituents where such groups are mentioned. Compounds of preference specifically include the following molecules which are readily synthesized and show advantageous biological properties both in their free base form and
 15 in the form of their pharmaceutically acceptable salts:

2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide radical

20 2-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide

4-(4-carbamoyl-1H-benzimidazol-2-yl)-1-oxyl-2,2,5,5-tetramethyl-pyrrolidine-3-carboxylic acid methyl ester radical

25 4-(4-carbamoyl-1H-benzimidazol-2-yl)-2,2,5,5-tetramethyl-pyrrolidine-3-carboxylic acid methyl ester

2-(4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide radical

2-(4-bromo-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide
 30

2-(1-oxyl-4-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide radical

2-(4-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide

35 2-[1-oxyl-2,2,5,5-tetramethyl-4-(3-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrol-3yl]-1H-benzimidazole-4-carboxylic acid amide radical

- 5 2-[2,2,5,5-tetramethyl-4-(3-trifluoromethyl-phenyl)-2,5-dihydro-1H-pyrrol-3yl]-1H-benzimidazole-4-carboxylic acid amide
- 2-[4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 10 2-[4-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- 2-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide
- 2-(1-acetyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide
- 15 2-(1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide
- 2-[4-(dibenzofuran-4-yl)-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 20 2-[4-(dibenzofuran-4-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- (1-hydroxy-2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-benzimidazole-4-carboxylic acid amide
- 25 2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-benzimidazole-4-carboxylic acid amide
- 2-[4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 30 2-[4-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- 2-[3-methoxy-4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 35

- 5 2-[3-methoxy-4-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- 2-(5-oxyl-4,4,6,6-tetramethyl-4,6-dihydro-5H-thieno[2,3-c]pyrrol-2-yl)-1H-benzimidazole-4-carboxylic acid amide
- 10 radical
- 2-(4,4,6,6-tetramethyl-4,6-dihydro-5H-thieno[2,3-c]pyrrol-2-yl)-1H-benzimidazole-4-carboxylic acid amide
- 2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid isopropylamide radical
- 15 2-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid isopropylamide
- 1-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl-methyl)-1H-benzimidazole-4-carboxylic acid amide radical
- 1-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-benzimidazole-4-carboxylic acid amide and its dihydrochloride salt.
- 20

A further object of the present invention are processes to obtain the compounds according to the general formula (I).
 25 Such processes include reactions of suitably substituted carboxamides of the general formula (IV) - where

R¹ has the meaning as stated above -
 with heterocyclic derivatives of the general formulae (V) or (VI) - where

30 R², Y, Z and n have the meaning as stated above.

The carboxamides of general formula (IV) which are used as starting materials are known or can be prepared by known methods. One method is shown in reaction scheme B (see Figure 3). The same reaction scheme also shows the synthesis of the
 35 compounds of the general formula (I).

The condensation of carboxamides of the general formula (IV) with the heterocyclic molecules of general formula (V) or (VI) lead to the benzimidazole ring closure while also ensur-

5 ing the suitable substitution of the benzimidazole ring. This reaction can be accomplished in the presence of a suitable organic solvent such as toluene, benzene, chloroform etc. The optimal solvent depends also on the substituents of the benzimidazole ring. The reaction takes place normally under gentle heating at 20 to 80 °C. Isolation and purification of the products can be usually achieved by known methods.

10 Some compounds of the general formula (I) are sparingly soluble in water but they form pharmaceutically acceptable water-soluble salts with acids as already indicated above. Purification can be accomplished by way of salt-formation.

15 A further object of the present invention are pharmaceutical compositions comprising as an active ingredient compounds of the general formula (I) or their pharmaceutically acceptable salts. The present invention includes formulations comprising compounds of the general formula (I) in either of their possible forms (Ia), (Ib), (Ic) and (Id). The drugs can be administered orally in solid or liquid forms, transdermally, in different injectable forms or infusions, or any other form such as sublingual, pernasal, rectal. The pharmaceutical formulations are prepared and formulated accordingly.

20 Yet other objects of the present invention are methods of treatment of patients in need of such treatment where there is need for scavenging damages caused by ROS or RNS events or of PARP-inhibition or both by way of administering an effective amount of a compound of the general formula (I) in an adequate dosage form containing the effective dose. Typical of such damages are for example the following diseases which can be treated or prohibited by way of administration of effective amounts of compounds of the general formula (I) or their salts: coronary diseases, ischemia, inflammation. They may be used to enhance killing of tumour cells on the course of radiotherapy or chemotherapy.

5 The doses which can be used for the above purpose vary to a high degree depending on the intended use and the molecule and its substituents, employed.

10 Yet another object of the present invention is the process to produce the pharmaceutical compositions comprising as active ingredient a compound of the general formula (I) in either of their possible forms (Ia), (Ib), (Ic) and (Id) to obtain formulations which can be administered for scavanging damages caused by ROS or RNS events or of PARP-inhibition or both. The formulation for oral, injectable, parenteral, rec-
15 tal, transdermal or other uses into tablets, pellets, solutions, injectables, patches etc. can be achieved principally in the known manner with usual pharmaceutical additives .

5 Details of the invention are disclosed in the following examples without the intention of limitation.

I. Chemical Examples

10 First general methods of synthesis of the molecules are described followed by tables with the data related to compounds synthesized.

 General methods for preparing compounds of general formula (I) are illustrated in the reaction scheme B (see Figure 3). The meaning of the substituents is the same as indicated above in the specification.

15

EXAMPLE I.1

 Synthesis of 2-amino-3-nitrobenzamide of general formula (III)

20 A suspension of 2-amino-3-nitrobenzoic acid (1.82 g, 10.0 mmol) heated under reflux for 3 hours in thionyl chloride (10 mL) and the thionyl chloride is removed by vacuum distillation. The residual solid is suspended in THF (20 mL) and 25 % aq. ammonia solution (20 mL) is added in portions with stirring within 15 min. The mixture is allowed to stay overnight, 25 the orange precipitate is filtered and air-dried to give 2-amino-3-nitrobenzamide (900 mg, 49 %); mp 238-239 °C; ν max (cm^{-1}) 3420, 3180, 1680, 1580, 1555.

EXAMPLE I.2

30 A mixture of 2-amino-3-nitrobenzoic acid (1.82 g, 10.0 mmol) and 1,1'-carbonyldiimidazole (1.62g 10.0 mmol) is refluxed for 30 min in dry THF (40 mL) and a 25 % aqueous ammonia solution (20 mL) or the corresponding primary or secondary amine is added in one portion with stirring. The mixture is allowed to stay overnight, the orange precipitate is filtered 35 and air-dried to give 2-amino-3-nitrobenzamide (1.52 g, 84 %) or 2-amino-3-nitro-(N-substituted)-benzamide.

5 EXAMPLE I.3

Synthesis of 2,3-diamino-benzamides of the general formula (IV)

Pd/C (200 mg) is added to a stirred mixture of 2-amino-3-nitrobenzamide (1.81 g, 10.0 mmol) or 2-amino-3-nitro-(N-substituted)-benzamide and ammonium-formiate (3.78 g, 0.06 mol) in methanol (40 mL) or some other appropriate solvent and the mixture is stirred at 40 °C for 2 hours. The mixture is then filtered through Celite, washed with methanol (40 mL) or the used solvent, evaporated and the residue is purified by way of crystallization or flash column chromatography to give 2,3-diaminobenzamide as a pale brown light sensitive solid (800 mg, 53 %), mp 103-105 °C; ν_{\max} (cm⁻¹) 3330, 3170, 1630, 1600, MS m/z (%): 151 (M⁺, 70), 134 (72), 106 (100) 79 (38).

The same method can be used for 2,3-diamino-(N-substituted) benzamides.

20 EXAMPLE I.4

Synthesis of 2-substituted-4-carboxamidobenzimidazoles (Method A)

25 A mixture of 2,3-diamino-benzamide (1.51 g, 10.0 mmol) or a 2,3-diamino-(N-substituted)-benzamide (10.0 mmol) and a suitable paramagnetic aldehyde (of general formula V) or diamagnetic aldehyde (of general formula VI) (10.0 mol), and toluene-*p*-sulfonic acid monohydrate (95 mg, 0.5 mmol) is refluxed in toluene (40 mL) or in an other appropriate solvent till all the starting compounds are consumed (4-6 hours) under Dean and Stark apparatus. Then the solvent is evaporated in vacuo, the residue dissolved in CHCl₃ (50 mL) or in some other halogenated solvent, and an appropriate oxidant such as activated MnO₂ (4.30 g, 50.0 mmol) is added and the mixture is stirred and refluxed for about 6 hours. The mixture was filtered through Celite, evaporated and the residue was purified

5 by flash column chromatography ($\text{CHCl}_3/\text{Et}_2\text{O}$ or $\text{CHCl}_3/\text{MeOH}$) or crystallization to give compound Ia or Ib (yield: 39-73 %).

The aldehydes used are known see e.g.: Hideg et al. *Synthesis* (1980) 911-914; (1991) 616-620; Csekő et al. *Can. J. Chem.* (1985) 63 940-943; Sár, P. C. et al. *Synth. Comm.*,
10 (1995) 25, 2929-2940; Kálai et al. *Synthesis* (1998) 1476-1482; (1999) 973-980; Hankovszky et al. *Synthesis* (1980) 914-916.

EXAMPLE I.5

General method for reducing nitroxide radicals of the
15 general formula Ia) ($\text{Q} = \text{O}^\cdot$) to diamagnetic alicyclic secondary amines of the general formula (Ib) ($\text{Q} = \text{H}$) (Method B).

Upon addition of iron powder (224 mg, 4.0 mmol) to a stirred solution of the paramagnetic compound of general formula (Ia) (2.0 mmol) in acetic acid (7 ml) and gentle heating
20 (max. 60 °C) for 30 min., the reaction mixture is diluted with water (20 mL) and filtrated. The filtrate is basified with solid potassium carbonate, extracted with chloroform (2x20 ml), dried and evaporated. The residue is purified by
flash chromatography ($\text{CHCl}_3/\text{MeOH}$) or acidified with ethanol
25 saturated with hydrochloride gas. The white crystalline hydrochloride salt of the product of the general formula (Ib) is precipitated from EtOH/Et₂O solution (yield: 48-65 %).

EXAMPLE I.6

30 Method for reducing nitroxide radicals of general formula (Ia) ($\text{Q} = \text{O}^\cdot$) to diamagnetic alicyclic N-hydroxylamines of general formula (Ic) ($\text{Q} = \text{OH}$) (Method C):

A solution of the paramagnetic compound of general formula (Ia) (1.0 mmol) in ethanol saturated with hydrochloride
35 gas (10 ml) is refluxed for 1 hour, then diluted with diethyl ether to precipitate the diamagnetic hydroxylamine HCl salt of the general formula (Ic). The basic compound is obtained in white solid from EtOH/Et₂O solution (yield: 53-64 %).

5

EXAMPLE I.7

4-Carboxamido-1-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-ylmethyl)benzimidazole.

10 The mixture of 3-carboxamido-benzimidazole (805 mg, 5.0 mmol), 3-bromomethyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole (1.16 g, 5.0) mmol and potassium hydroxide (280 mg, 5.0 mmol) is refluxed in methanol or other suitable solvent (25 mL) for about 3 hours. The inorganic salt is filtered off, the filtrate evaporated and the residue purified by flash column chromatography (CHCl₃/Et₂O) to give 970 mg (62 %) of the
15 title compound.

In accordance with the above general methods a series of compounds of general formula (I) was prepared. The compounds with their formulae, characteristics as well as PARP inhibiting
20 and antioxidative effects are shown in Table I.

II. BIOLOGICAL ACTIVITY STUDIES

Example II.1.

25 Assay to test inhibitory effects of benzimidazole derivatives on PARP enzyme in vitro.

Poly-ADP-ribose polymerase was isolated from rat liver based on a known method (*Anal Biochem* 1995, 227, 1-13; 2000, 59, 937-945). The potential inhibitory effect of benzimidazole derivatives were tested in this assay system. The PARP activity was determined in 130 µl reaction mixture contained 100 mM Tris-HCl buffer, pH 8.0, 10 mM MgCl₂, 10 % glycerol, 1.5 mM DTT, 1 mM [Adenine-2,8-³H] NAD⁺ (4.500 cpm/nmol), 10 µg activated DNA and 10 µg histones. The incubation time was 15 minutes, and the reaction was stopped by addition of
35 trichloroacetic acid (8 %). After addition of 0.5 mg albumin, precipitation was allowed to proceed for at least 20 minutes on ice, and the insoluble material was collected on a glass filter washed with 5 % perchloric acid. The protein-bound ra-

5 dioactivity was determined by a LS-200 Beckman scintillation counter. Data shown in Table I are IC_{50} values in nM.

Example II.2.

Protecting effect of benzimidazole derivatives against H_2O_2 induced cell death determined in WRL-68 human liver cell
10 line. (Antiox 1, % of protection comparing to control values):

Cell culture. WRL-68 human liver cell line was from American Type Culture Collection (Rockville, MD). Cell lines were grown in humidified 5 % CO_2 atmosphere at 37 °C and main-
15 tained in culture as monolayer adherent cells in Dulbecco's Modified Eagle's Medium containing 1% antibiotic-antimycotic solution (Sigma, St. Louis, MO) and 10 % fetal calf serum. Cells were passaged at intervals of 3 days.

Detection of cell survival. Cells were seeded into 96-
20 well plates at a starting density of 2.5×10^4 cell/well and cultured overnight in humidified 5 % CO_2 atmosphere at 37 °C. The following day H_2O_2 was added to the medium at the indicated concentrations either alone or in the presence of 10 μM of the protecting agent (benzimidazole derivatives). Three hours
25 later the medium was removed and 0.5 % of the water soluble mitochondrial dye (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT⁺) was added. Incubation was continued for 3 more hours, the medium was removed and the metabolically reduced water- insoluble blue formazan dye was solubilised by
30 acidic isopropanol. Optical densities were determined by an Anthos Labtech 2010 ELISA reader (Wien, Austria) at 550 nm wavelength. All experiments were run in at least 6 parallels and repeated 3 times. Data of Table ??? are the concentration of benzimidazoles (in nM) at which the rate of H_2O_2 induced
35 cell death was inhibited with 50 %.

5 **Example II.3.**

Hydroxyl radical scavenging of benzimidazole derivatives
(Antiox 2):

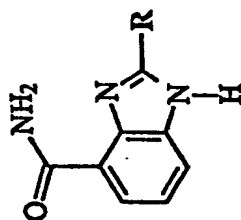
10 Hydroxyl radical formation was detected using the oxidant-sensitive non-fluorescent probe benzoic acid which is hydroxylated to 2, 3 or 4-hydroxy-benzoic acid (*J. Biol. Chem.* (1996) 271 40-47). Hydroxylation of benzoic acid results in the appearance of intensive fluorescence which makes possible the fluorescence spectroscopic monitoring of the hydroxylation reactions excitation 305 nm emission 407 nm. The reaction was
15 studied in a 2.5 ml reaction volumes containing 20 mM potassium phosphate buffer (pH 6.8) 0.1 mM benzoic acid, 0.1 mM H_2O_2 and 20 μM Fe^{2+} -EDTA. Data of Table ??? show the concentration of benzimidazoles (in nM) at which the rate of hydroxyl radical induced hydroxylation is inhibited with 50 % .

20

Statistical analysis.

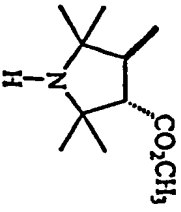
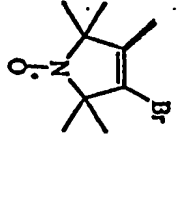
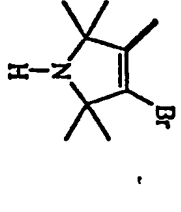
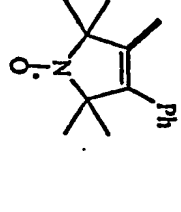
Data were presented as means \pm S.E.M. For multiple comparison of groups ANOVA was used. Statistical difference between groups was established by paired or unpaired Student's t test,
25 with Bonferroni correction.

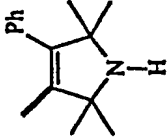
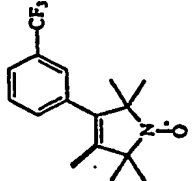
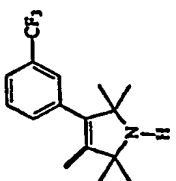
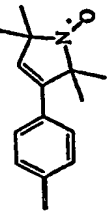
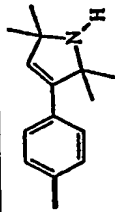
TABLE I.

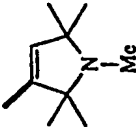
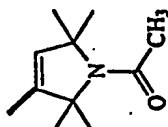
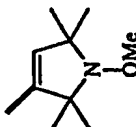
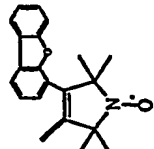
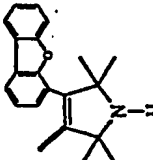
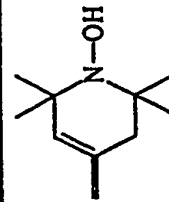


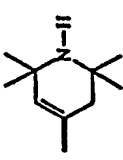
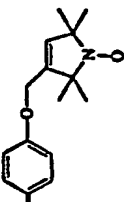
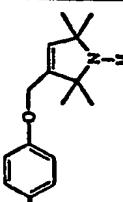
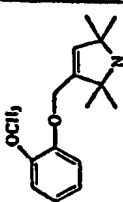
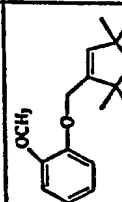
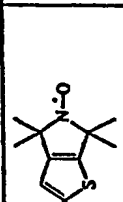
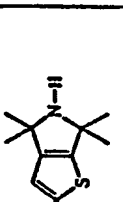
Compd.	R	Method (Yield)	mp °C	m/z (EI)	Formula	PARP IC ₅₀ nM	Antiox1 IC ₅₀ nM	Antiox2 IC ₅₀ nM
1		A (51 %)	248-250	299 (M ⁺ , 19), 269 (37), 223 (51), 41 (100)	C ₁₆ H ₁₉ N ₄ O ₂ 299.35	721	23.3	0.48
2		B (65 %)	239-241	284 (M ⁺ , 1), 269 (100), 252 (91), 224 (14)	C ₁₆ H ₂₀ N ₄ O 284.36	345	92.1	2.1
3		A (55 %)	255-257	359 (M ⁺ , 12), 246 (60), 215 (62), 41 (100)	C ₁₈ H ₂₃ N ₄ O ₄ 359.40	ND*	85.9	0.9

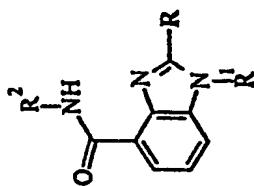
*ND: not determined

4		B (59 %)	> 260	344 (M ⁺ , 1), 312 (6), 246 (100), 229 (54)	C ₁₈ H ₂₄ N ₄ O ₃ 344.41	216	43.2	3.1
5		A (53 %)	142-145	377/379 (M ⁺ , 13/13), 363/365 (36/36), 268(100), 251 (82)	C ₁₆ H ₁₈ BrN ₄ O ₂ 378.24	201	13.0	2.8
6		B (65 %)	249-251	362/364 (M ⁺ , <1), 347/349 (63/63), 250 (48), 42 (100)	C ₁₆ H ₁₉ BrN ₄ O 363.25	137	16.7	3.4
7		A (57 %)	257-259	375 (M ⁺ , 11), 345 (27), 162 (93), 145 (100)	C ₂₂ H ₂₃ N ₄ O ₂ 375.45	1500	93.2	12.5

8		B (48 %)	256-258	360 (M ⁺ , 2), 345 (100), 328 (40), 285 (13)	C ₂₂ H ₂₄ N ₄ O 360.45	310	98.5	0.38
9		A (56 %)	253-255	443 (M ⁺ , 65), 413 (72), 398 (82), 381 (100)	C ₂₃ H ₂₂ F ₃ N ₄ O ₂ 443.44	149	17.3	11.2
10		B (50 %)	224-226 (2 HCl)	428 (M ⁺ , 2), 413 (100), 396 (46), 353 (11)	C ₂₃ H ₂₃ F ₃ N ₄ O 428.45	133	25.5	13.4
11		A (45 %)	254-256	375 (M ⁺ , 8), 345 (100), 327 (22), 237 (41)	C ₂₂ H ₂₃ N ₄ O ₂ 375.45	78	49	7.2
12		B (52 %)	149-151	360 (M ⁺ , <1), 345 (100), 328 (24), 313 (6)	C ₂₂ H ₂₄ N ₄ O 360.45	98	33.2	4.5

13		A (61 %)	173-175	298 (M ⁺ , 4), 283 (47), 269 (98), 252 (100)	C ₁₇ H ₂₂ N ₄ O 298.38	42	42	73
14		A (73 %)	139-141	326 (M ⁺ , 10), 311 (52), 252 (62), 43 (100)	C ₁₈ H ₂₂ N ₄ O ₂ 326.39	49	66.8	81
15		A (49 %)	> 260	314 (M ⁺ , 11), 299 (100), 282 (22), 268 (18)	C ₁₇ H ₂₂ N ₄ O ₂ 314.38	61	68.3	113
16		A (44 %) C (64 %)	160-162 195-197	465 (M ⁺ , 77), 451 (40), 435 (100), 420 (84)	C ₂₈ H ₂₅ N ₄ O ₃ 465.53	1800	79.15	53
17		B (55 %)	223-225	450 (M ⁺ , 2), 435 (100), 418 (26), 375 (11)	C ₂₈ H ₂₆ N ₄ O ₂ 450.54	8200	48.0	70
18		A, C (53 %)	235-237	314 (M ⁺ , 14), 299 (100), 283 (72), 237 (53)	C ₁₇ H ₂₃ ClN ₄ O ₂ 350.85	26	23	9.6

19		B (45 %)	> 260	298 (M ⁺ , 23), 283 (81), 266 (29), 42 (100)	C ₁₇ H ₂₂ N ₄ O 298.38	14	83	1.6
20		A (43 %) C (60 %)	144-146 174-176	405 (M ⁺ , 12), 375 (19), 108 (75), 41 (100)	C ₂₃ H ₂₅ N ₄ O ₃ 405.47	564	40.0	13.2
21		B (57 %)	198-200	390 (M ⁺ , 2), 375 (29), 122 (65), 108 (100)	C ₂₃ H ₂₆ N ₄ O ₂ 390.48	572	29.2	4.3
22		A (46 %)	244-246	435 (M ⁺ , 10), 405 (10), 122 (81), 108 (100)	C ₂₄ H ₂₇ N ₄ O ₄ 435.50	472	27.3	14.1
23		B (40 %)	234-235	420 (M ⁺ , 3), 405 (25), 122 (71), 108 (100)	C ₂₄ H ₂₈ N ₄ O ₃ 420.51	432	0.4	3.8
24		A (39 %)	> 260	355 (M ⁺ , 10), 341 (56), 325 (100), 308 (34)	C ₁₈ H ₁₉ N ₄ O ₂ S 355.43	3400	7.6	27
25		B (55 %)	> 260	340 (M ⁺ , 6), 325 (100), 308 (53), 280 (10)	C ₁₈ H ₂₀ N ₄ O ₂ S 340.44	354	5.2	10.5



Compd.	R	R ¹	R ²	Method (Yield)	mp °C	m/z (EI)	Formula	PARP IC ₅₀ nM	Antiox 1 IC ₅₀ nM	Antiox 2 IC ₅₀ nM
26		H	<i>i</i> -Pr	A (46 %)	241-243	341 (M ⁺ , 30), 327 (45), 311 (72), 223 (100)	C ₁₉ H ₂₅ N ₄ O ₂ 341.43	10000>	30	2.1
27		H	<i>i</i> -Pr	B (51 %)	231-233	326 (M ⁺ , <1), 311 (100), 252 (21), 224 (4)	C ₁₉ H ₂₆ N ₄ O 326.44	10000>	23	2.3
28	H		H	(62 %)	247-249	313 (M ⁺ , 48), 299 (15), 283 (24), 41 (100)	C ₁₆ H ₂₀ N ₃ O 270.35	10000>	32	1.8

5

CLAIMS

1. Compounds of the formula (I) and their pharmaceutically acceptable or technically applicable acid salts - where in the formula

10

R^1 represents hydrogen, an alkyl or alkoxy group

R^2 represents hydrogen, an alkyl, carboxyl, alkoxy carbonyl, carboxamido or aryl group or a hetero aryl group

15

R^3 represents hydrogen, alkyl, aryl-methylene, or aryl group

Y is a valency bond, a straight or branched alkene group, carbonylaminoalkene group containing 1 to 4 carbon atoms, spaced or not spaced by an arylene group

20

n is zero or 1

Q represents hydrogen, a hydroxyl group or oxygen radical (O \cdot)

Z represents a single or double bond.

25

2. Compounds according to claim 1 where the substituents contain C₁₋₄ alkyl as alkyl, C₁₋₄ alkoxy as alkoxy, C₁₋₄ alkoxy carbonyl as alkoxy carbonyl, 6 or 12 membered aryl as aryl, piperidine, pyrrole or pyrrolidine groups as heteroaryl groups, a C₁₋₄ alkene as alkene, 6 or 12 membered arylene as arylene groups in any of the substituents where such groups are mentioned.

30

3. The following compounds according to claim 1 and their salts formed with pharmaceutically acceptable or technologically useful acid salts:

35

2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid amide radical

5 4-(4-carbamoyl-1*H*-benzimidazol-2-yl)-1-oxyl-2,2,5,5-tetramethyl-pyrrolidine-3-carboxylic acid methyl ester radical

4-(4-carbamoyl-1*H*-benzimidazol-2-yl)-2,2,5,5-tetramethyl-pyrrolidine-3-carboxylic acid methyl ester

10 2-(4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide radical

2-(4-bromo-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide

15 2-(1-oxyl-4-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide radical

2-(4-phenyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide

20 2-[1-oxyl-2,2,5,5-tetramethyl-4-(3-trifluoromethyl-phenyl)-2,5-dihydro-1*H*-pyrrol-3yl]-1*H*-benzimidazole-4-carboxylic acid amide radical

25 2-[2,2,5,5-tetramethyl-4-(3-trifluoromethyl-phenyl)-2,5-dihydro-1*H*-pyrrol-3yl]-1*H*-benzimidazole-4-carboxylic acid amide

2-[4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-phenyl]-1*H*-benzimidazole-4-carboxylic acid amide radical

30 2-[4-(2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-phenyl]-1*H*-benzimidazole-4-carboxylic acid amide

2-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide

2-(1-acetyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide

35 2-(1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3yl)-1*H*-benzimidazole-4-carboxylic acid amide

- 5 2-[4-(dibenzofuran-4-yl)-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 2-[4-(dibenzofuran-4-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- 10 (1-hydroxy-2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-benzimidazole-4-carboxylic acid amide
- 2-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-benzimidazole-4-carboxylic acid amide
- 15 2-[4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 2-[4-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- 20 2-[3-methoxy-4-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide radical
- 25 2-[3-methoxy-4-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3ylmethoxy)-phenyl]-1H-benzimidazole-4-carboxylic acid amide
- 2-(5-oxyl-4,4,6,6-tetramethyl-4,6-dihydro-5H-thieno[2,3-c]pyrrol-2-yl)-1H-benzimidazole-4-carboxylic acid amide radical
- 30 2-(4,4,6,6-tetramethyl-4,6-dihydro-5H-thieno[2,3-c]pyrrol-2-yl)-1H-benzimidazole-4-carboxylic acid amide
- 2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid isopropylamide radical
- 35 2-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-benzimidazole-4-carboxylic acid isopropylamide

5 2-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl)-1H-
benzimidazole-4-carboxylic acid isopropylamide
1-(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3yl-methyl)-
1H-benzimidazole-4-carboxylic acid amide radical;
1-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydro-pyridin-4-yl)-
10 1H-benzimidazole-4-carboxylic acid amide.

4. Compounds according to any of claims 1 to 3 in the form
of their salts formed with inorganic or organic acids
said salts being technologically useful such as oxalates
15 or pharmacologically acceptable such as hydrochlorides,
hydrobromides, sulphates, phosphates, phosphites, bo-
rates, lactates, ascorbates, acetates, fumarates, for-
mates, tosylates, tartarates, maleates, citrates, gluco-
nates, besylates etc.

20 5. Pharmaceutical compositions comprising as active ingredi-
ents in an effective dose compounds according to any of
the claims 1 to 4 or their pharmaceutically acceptable
salts for the treatment of diseases which can be favoura-
25 bly influenced by PARP inhibition and/or scavanging oxi-
dative stress.

6. Pharmaceutical compositions according to claim 5 compris-
ing as active ingredients in an effective dose compounds
30 according to any of the claims 1 to 4 or their pharmaceu-
tically acceptable salts for treatment of ischemia/reper-
fusion, inflammations and/or potentiation of cancer the-
rapies.

35 7. Pharmaceutical compositions according to claim 5 or 6
which appear in formulations for oral, transdermal, par-
enteral, intramuscular, intravenous administration e.g.
in the following forms: tablets, injections, solutions,

5 suppositories, patches, suspensions etc.

8. Process for the preparation of compounds of the general formula (I) and their pharmaceutically acceptable or technically applicable acid salts - where in the formula

10 R^1 represents hydrogen, an alkyl or alkoxy group

R^2 represents hydrogen, an alkyl, carboxyl, alkoxy carbonyl, carboxamido or aryl group or a hetero-aryl group

15 R^3 represents hydrogen, alkyl, aryl-methylene or aryl group

Y is a valency bond, a straight or branched alkene group, carbonylaminoalkene group containing 1 to 4 carbon atoms, spaced or not spaced by an arylene group

20 n is zero or 1

Q represents hydrogen, a hydroxyl group or oxygen radical (O \cdot)

Z represents a single or double bond

25 characterised by reacting carboxamides of the general formula (IV) - where

R^1 has the meaning as stated above -

with heterocyclic derivatives of the general formulae (V) or (VI) - where

R^2 , Y, Z and n have the meaning as stated above.

30

9. Process according to claim 8 characterised by preparing any of the compounds of claim 3 or its technologically useful salts such as oxalates or pharmacologically acceptable salts such as hydrochlorides, hydrobromides, sulphates, phosphates, phosphites, borates, lactates, ascorbates, acetates, fumarates, formiates, tosylates, tartarates, maleates, citrates, gluconates, besylates.

35

5 10. Method of treatment of diseases which are based on PARP
activation or are caused by Reactive Oxidative Species
(ROS) and Reactive Nitrogen Species (RNS) specifically
cases of ischemia/reperfusion, inflammation, unfavourable
reaction on the course of radiotherapy or chemotherapy by
10 administration to the patient in need of such treatment
an effective dose of at least one compound of the general
formula I or its pharmaceutically acceptable salt - where
in the formula

R¹ represents hydrogen, an alkyl or alkoxy group

15 R² represents hydrogen, an alkyl, carboxyl, alkoxy
carbonyl, carboxamido or aryl group or a hetero-
aryl group

R³ represents hydrogen, alkyl, aryl-methylene or
aryl group

20 Y is a valency bond, a straight or branched alkene
group, carbonylaminoalkene group containing 1 to 4
carbon atoms, spaced or not spaced by an, arylene
group

n is zero or 1

25 Q represents hydrogen, a hydroxyl group or oxygen
radical (O[·])

Z represents a single or double bond -
in the form of a dosage form comprising said effective
dose.

30

11. Process for the preparation of pharmaceutical formula-
tions which can be used for the treatment of diseases
which are based on PARP activation or are caused by Reac-
tive Oxidative Species (ROS) and Reactive Nitrogen Spe-
cies (RNS) such as ischemia/reperfusion, inflammation,
35 unfavourable reaction on the course of radiotherapy or
chemotherapy by formulation of compounds of the general
formula (I) or its salts - where in the formula

R¹ represents hydrogen, an alkyl or alkoxy group

- 5 R^2 represents hydrogen, an alkyl, carboxyl, alkoxy
 carbonyl, carboxamido or aryl group or a hetero-
 aryl group
- R^3 represents hydrogen, alkyl, aryl-methylene or
 aryl group
- 10 Y is a valency bond, a straight or branched alkene
 group, carbonylaminoalkene group containing 1 to 4
 carbon atoms, spaced or not spaced by an arylene
 group
- n is zero or 1
- 15 Q represents hydrogen, a hydroxyl group or oxygen
 radical ($O\cdot$)
- Z represents a single or double bond -
 with usual additives into ready to use dosage forms by
 methods known per se.

20

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For the applicants:



Dr Eva Somfai
patent attorney

25

ABSTRACTS

NEW PHARMACEUTICALS

Applicants and inventors: DR. HIDEG Kálmán 45%,
Dr. KÁLAI Tamás 10%, Dr. SÜMEGI Balázs 45%

New compounds of the general formula (I), their pharmaceutically acceptable or technically applicable acid salts, processes for their preparation, compositions comprising the same, methods for their use as active ingredients of medicines and processes for the preparation of said medicines. In the general formula

R^1 represents hydrogen, an alkyl or alkoxy group

R^2 represents hydrogen, an alkyl, carboxyl, alkoxy carbonyl, carboxamido or aryl group or a hetero aryl group

R^3 represents hydrogen, alkyl, aryl-methylene, or aryl group

Y is a valency bond, a straight or branched alkene group, carbonylaminoalkene group containing 1 to 4 carbon atoms, spaced or not spaced by an arylene group

n is zero or 1

Q represents hydrogen, a hydroxyl group or oxygen radical ($O\cdot$)

Z represents a single or double bond.

The new compounds can be used for the treatment of diseases which are based on PARP activation or are caused by Reactive Oxidative Species (ROS) and Reactive Nitrogen Species (RNS) such as ischemia/reperfusion, inflammation, unfavourable reaction on the course of radiotherapy or chemotherapy.

Figure I.

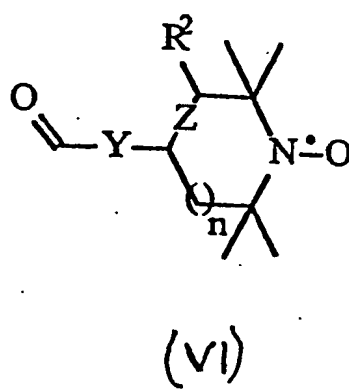
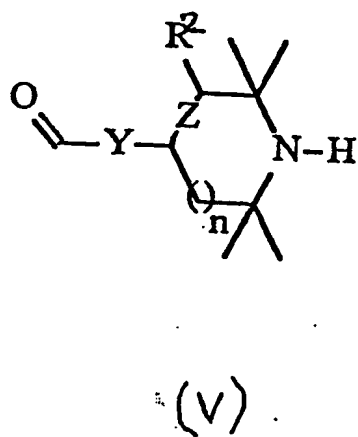
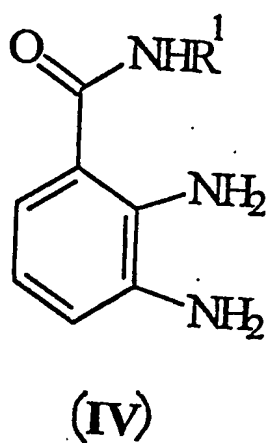
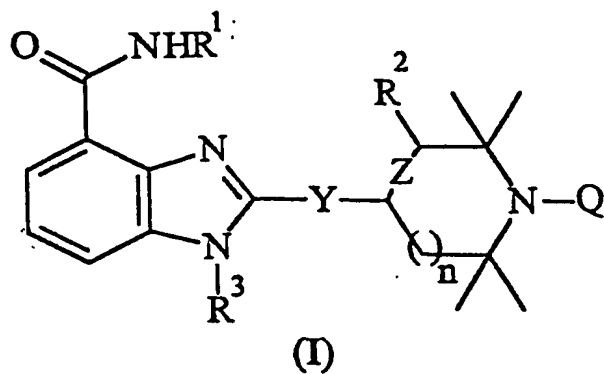


FIGURE 1

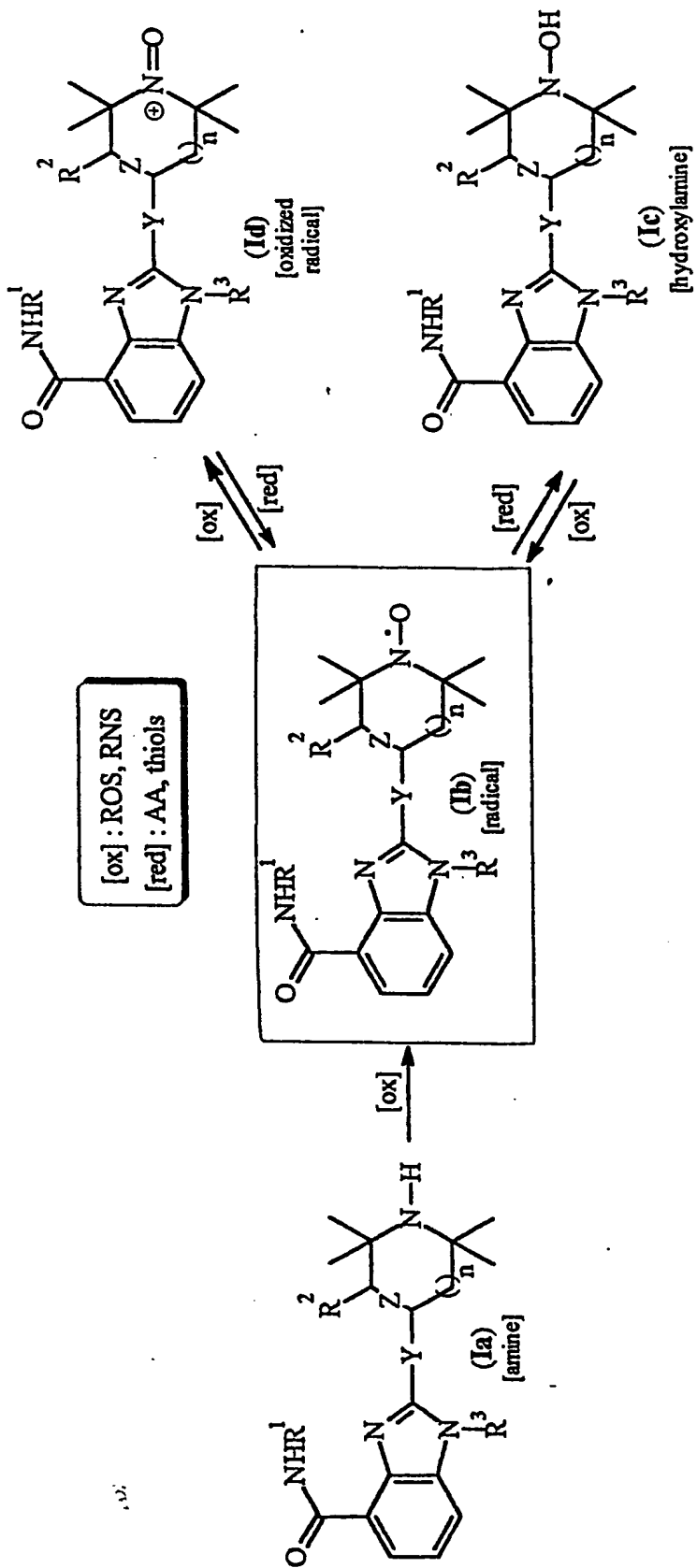


FIGURE 2

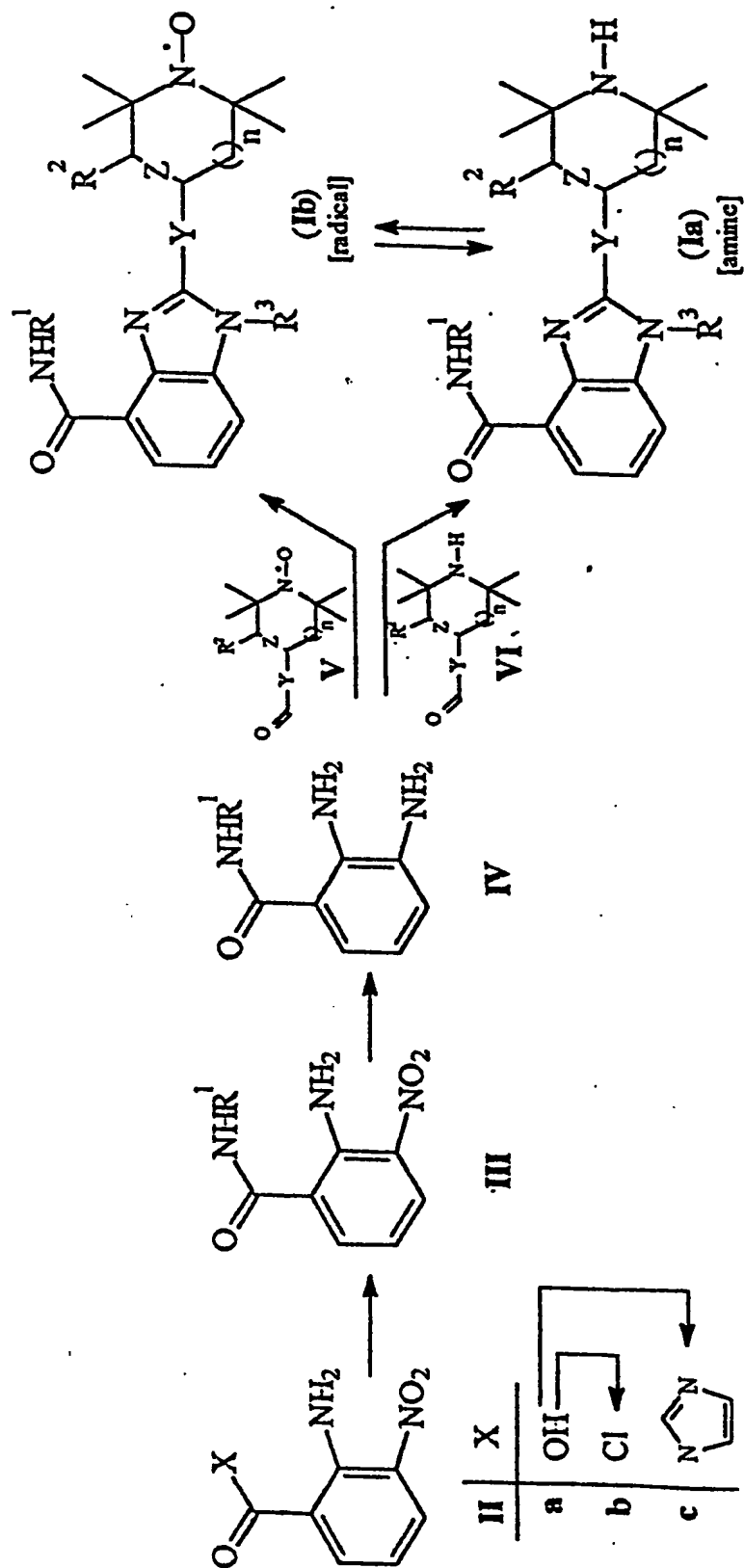


FIGURE 3